COMPOSITIONS AND METHODS FOR TREATMENT OF LUNG FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 16/922,119 filed Jul. 7, 2020, which claims priority to U.S. Ser. No. 15/927,575 filed Mar. 21, 2018, which claims priority to and benefit of U.S. Provisional Application No. 62/474,739, filed Mar. 22, 2017, the contents of each are incorporated in their entirety for all purposes.

GOVERNMENT SUPPORT CLAUSE

[0002] This invention was made with government support under HL142210, HL154105, HL116226 and HL125954 awarded by the National Institutes of Health. The government has certain rights in this invention.

BACKGROUND

[0003] Cystic fibrosis (CF) is an autosomal recessive disorder that affects approximately 30,000 individuals in the United States. The primary defect results from mutations of the cystic fibrosis transmembrane conductance regulator gene, which codes for the CFTR chloride channel. The protein is expressed predominantly on the apical surface of epithelial cells throughout the body (although low level expression has been detected in other tissues). Over 2,000 disease causing mutations have been identified in the CFTR gene, with the majority of patients (~90%) exhibiting at least one allele with the F508del mutation. Disease causing mutations fall into 5 classifications that result in abnormal CFTR protein that is either truncated, misprocessed/mislocalized, lacking channel gating function, or malformed due to improper gene splicing. With advances in new-born and other screenings, CF is usually diagnosed at birth. Although the determinants of disease are well characterized, forecasting disease progression has been extremely difficult and as of yet unsuccessful.

[0004] Care for CF patients has advanced rapidly over the past two decades, with an increase in patient longevity and quality of life that is unprecedented. The reasons for these improvements include a number of factors. First, the Cystic Fibrosis Foundation (CFF) has been tracking outcomes for nearly 50 years through their robust Patient Registry (CFF-PR), which includes patient data from nearly all CF patients in the US (individuals receiving care at accredited US CF centers), allowing assessment of outcomes and treatment responses. Next, there have been dramatic advances in new CF therapeutics (e.g. the development of recombinant human DNase, inhaled antibiotics including dissolved and dry powder tobramycin, aztreonam, hypertonic saline, low dose azithromycin to control inflammation, FDA approval of standardized pancreatic enzyme replacement, and most recently genotype-specific CFTR modulators such as KALYDECO® (4) and ORKAMBI® (5), and more recently TRIKAFTA® (6). In tandem with these new treatments, there has been a focus on the development of CF care guidelines and standardization of care across accredited CF care centers. This has helped to 'raise all boats' in the CF care community, accompanied by center-specific data to drive local quality improvement. Finally, understanding of disease severity predictors has advanced significantly, including the importance of weight in predicting pulmonary stability, the contribution of chronic *Pseudomonas* and MRSA infection to pulmonary decline and mortality, and the relationship between poorly controlled diabetes and disease progression. Indeed, these advancements have increased the median survival of CF patients to 41 years (CFF-PR—2014), and nearly 50% of CF patients alive today are adults. However, despite this impressive progress in CF care, lung function decline continues even in patients being treated with the best modulators of CFTR currently available. (See, e.g., Nataliya Volkova et al., Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. JCF. DOI: 10.1016/j.jcf.2019.05.015.)

[0005] Accompanying the improvements in CF outcomes are a number of challenges that urgently require attention. There have been dramatic global improvements in the CF disease trajectory, but many patients have not fully benefited from the advancements described above. (FIG. **3**.) Indeed, the average age of death of CF patients in a given year has remained remarkably static, with most patients dying of CF lung disease during their third decade of life (CFF-PR 2014 statistics). The burden of care also remains a significant challenge, as most adolescents and young adults need to spend approximately two hours daily dedicated to therapies that maintain health. Adherence to complex care regimens is often untenable, and this has led to the need to 'personalize' care such that patients commit to daily therapies that are most likely to benefit them individually. These commitments increase during periods of instability, and treatment of PE remains highly interruptive to daily care and negatively impacts quality of life. They also are sentinel markers of disease progression, as 25% of CF patients fail to recover lung functions following PEs. The benefits of care improvements have also challenged the capacity to monitor CF lung disease and CF manifestations in other organs. Assessing the relative benefit of new therapies in the context of relatively normal lung function (as measured by routine spirometry) is particularly challenging for CF providers. This requires the development of more sensitive tools to identify subjects most likely to benefit from various interventions and to monitor the impact of new therapies added to care plans. Finally, the conduct of clinical trials to advance CF outcomes and interventions can no longer rely on standard outcome measures such as forced expiratory volume in 1 sec (FEV_1), as excessively large and/or long clinical trials are needed to demonstrate improvements in crude measurements such as lung function. Thus, the CF field stands at a crossroads, where the benefits of the past limit the capacity to advance therapies and personalize care when relying upon standard measures of disease status. The disclosed methods, in certain aspect, may be used to address these gaps, seeking to produce vertical advancement in disease monitoring and prediction through the use of advanced biostatistical modeling of lung function, which may be further enhanced via coupling with novel molecular biomarkers and/or imaging. The disclosed methods may be used to identify those patients most likely to benefit from various interventions, and allow clinicians to monitor responses to precise and personal interventions.

[0006] The natural history of the disease is well studied; but disease progression is not well understood. Pulmonary decline typically begins in adolescence, but current measures tend to follow rather than predict outcomes. For example, if a marker predicted disease instability and erratic